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Prognostic Factors Predictive of Survival and Local Recurrence for Extremity Soft Tissue Sarcoma

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Objective
The authors sought to identify prognostic factors in the management of extremity soft tissue sarcoma.

Summary Background Data
The surgical management of soft tissue sarcoma has evolved because of advances in therapy, resulting in increased limb preservation and quality of life. However, identifying a subset of patients most likely to benefit from adjuvant chemotherapy has been difficult to achieve.

Methods
A retrospective analysis of a prospective data base of 182 patients with extremity sarcomas from 1970 to 1992 was performed.

Results
A histologic diagnosis of Ewing's sarcoma, synovial sarcoma, and angiosarcoma was associated with a 13-fold increased risk of death compared with liposarcoma, fibrosarcoma, and malignant peripheral nerve sheath histologic types after having adjusted for the other prognostic factors ($p < 0.001$). In addition to histologic type, high-grade sarcomas ($p = 0.018$), sarcomas greater than 10 cm in size ($p = 0.006$), and age at diagnosis ($p = 0.016$) were found to be important prognostic factors for survival but not for local recurrence. For the first time to their knowledge, the authors showed that mean mitotic activity has prognostic value after having adjusted for other prognostic factors, such as grade ($p = 0.005$). The only prognostic factors predictive for local recurrence were whether the patient presented with locally recurrent disease ($p = 0.0001$) or had microscopically positive margins ($p = 0.052$).

Conclusions
The use of mitotic activity along with grade, size, histologic type, and age at diagnosis is prognostic for survival in extremity soft tissue sarcoma. The use of an objective pathologic feature, such as mean mitotic activity, is also useful in selecting patients for future systemic neoadjuvant or adjuvant trials and primary therapy.

Approximately 5800 new cases of soft tissue sarcoma are diagnosed annually in the United States.[1] Although there are more than 30 different histologic types of soft tissue sarcomas, most of these are grouped together because they are diagnosed, staged, and treated in a similar fashion. Surgery remains the principle modality of therapy in the management of soft tissue sarcomas. The importance of treating patients with such sarcomas with wide radical resections has been emphasized in many studies.[2-4] Currently, there is a debate about how wide the resection needs to be and when adjuvant modalities, such as radiation or chemotherapy, should be used. For low-grade sarcomas, a properly executed surgical resection continues to offer the best chance for cure. For high-grade sarcomas, the type and scope of surgical excision depends on whether external radiation therapy, interstitial irradiation, and/or systemic chemotherapy is used before or after surgery. Appropriate use of these modalities, in combination with surgery, has led to improved local control and functional preservation and resulted in higher cure rates.[3,5-11]

Identifying those patients most likely to benefit from adjuvant chemotherapy, however, has been difficult to achieve. In particular, in only 2 of 12 randomized studies, using doxorubicin-containing regimens, was there a demonstrated overall survival advantage for patients treated with chemotherapy.[12,13] In the National Cancer Institute trial, there was a significant difference in disease-free survival but not in survival for extremity lesions.[11] However, in that study, the control group (no chemotherapy) did extremely poorly. They also had significant cardiotoxicity secondary to doxorubicin. Moreover, in these 12 studies, 3 reported that survival was actually poorer in the patients treated with chemotherapy than in the patients not given adjuvant chemotherapy.[6,14,15] These results suggest that doxorubicin-based adjuvant therapy for soft tissue sarcomas at any primary site should be considered to be investigational. To date, the size and grade of the sarcoma continue to be the two most important clinical prognostic factors for survival in soft tissue sarcomas. It would be extremely beneficial to identify new prognostic factors that could influence clinical management and research. The present study serves to identify prognostic variables that could be used to select for patients most likely to benefit from adjuvant or neoadjuvant chemotherapy in future trials. Although limb-sparing surgery combined with radiation has been found to be equivalent to amputation in terms of overall survival, the influence of local recurrence on survival remains controversial.

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PATIENTS AND METHODS

From 1970 to 1992, 182 patients were referred to the Brigham and Women's Hospital and Dana Farber Cancer Institute with soft tissue sarcomas of the extremity. A retrospective analysis of this prospectively gathered group of patients was performed to determine the parameters governing survival and local recurrence of these patients. The median follow-up, from the time of presentation of the sarcoma up to December 1, 1992, was 105 months (range, 1 to 321 months).

Assessment

All patients were assessed according to the following tumor characteristics in a prospective fashion.

A. Characteristics of Primary Tumor
   1. Histologic type
   2. Grade (high, intermediate, or low)
   3. Mean and maximum number of mitoses per ten high-power fields (hpf)
   4. Tumor size (less than 5 cm, 5 to 10 cm, or greater than 10 cm)
   5. Location (proximal or distal)
   6. Primary or locally recurrent

B. Type of Treatment
   1. Type of initial biopsy (none, excisional, or incisional)
   2. Type of definitive resection (marginal, wide local, radical compartmental, or amputation)
   3. Margin of resection (clear, microscopic tumor, or macroscopic gross tumor)
   4. Closest margin in centimeters
   5. Adjuvant therapy (none, radiation therapy, or chemotherapy)

C. Disease Status and Survival
   1. Outcome (dead, alive with no evidence of disease, or alive with disease)
   2. Time to recurrence
   3. Type of recurrence (local or distant)
   4. Number of recurrences
   5. Ability to salvage after recurrence

The majority of the patients in this series was referred to us after a biopsy of the primary tumor or with a local recurrence after previous attempts at curative surgery. All histologic material was reviewed by a single pathologist at the Brigham and Women's Hospital (J.M.C.) and classified according to the histologic type, malignant grade, mitotic activity, and surgical margin. Grade was classified into low, intermediate, and high grades, based

Table 1. PREDICTORS OF SURVIVAL

Variable	Parameter Estimate	Standard Error	p value	Risk Ratio
Grade				
High *vs.* low	1.56	0.655	0.018	4.76
Size				
>10 cm *vs.* <5 cm	1.22	0.442	0.006	3.40
Histology				
Angio, synovial, Ewing's *vs.* lipo, fibro, peripheral nerve	2.54	0.505	0.0001	12.67
Age at diagnosis	0.028	0.012	0.015	1.03
Mean mitotic activity (mitoses/10 hpf)	0.055	0.020	0.005	1.06

hpf = high power fields.

on the NIH studies of Drs. Russell and Suit,[16] using the parameters of cellularity, pleomorphism, necrosis, and mitotic activity.

Statistical Analysis

Descriptive statistics are reported as proportions. Survival and local recurrence curves were constructed by the Kaplan–Meier product-limit method.[17] A modification to Greenwood's formula, making it more stable in the tail of the distribution,[18] was used to calculate the standard errors of the 12-year survival rates and probability free of local recurrence. The log-rank test[17] of survival analysis was used to compare the survival and local recurrence distributions of the various subgroups. Kaplan–Meier curves were plotted for graphic display of the treatment and prognostic factor effects, along with log-rank tests of the differences. Cox's proportional-hazards regression model,[19] using backward elimination,

Table 2. PREDICTORS OF LOCAL RECURRENCE

Variable	Parameter Estimate	Standard Error	p value	Risk Ratio
Local recurrence on presentation to BWH *vs.* primary disease on presentation	2	0.419	0.0001	7.37
Positive margin of resection *vs.* clean margin of resection	0.87	0.442	0.052	2.38

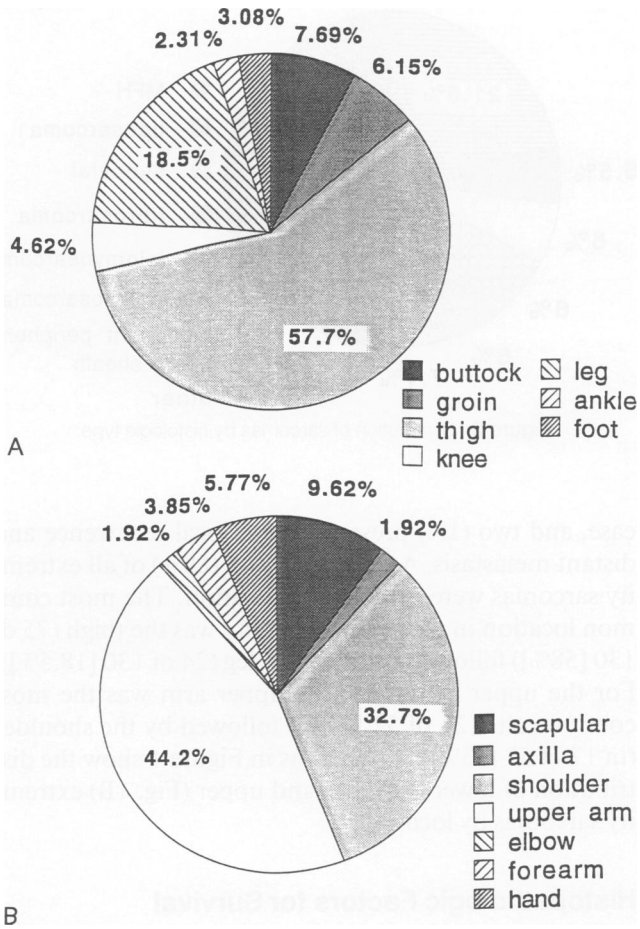

Figure 1. (A) Sites of lower extremity soft tissue sarcoma. (B) Sites of upper extremity soft tissue sarcoma.

was used to determine possible predictors of survival and local recurrence. A stepwise Cox proportional-hazards model, using backward elimination, was used to determine the most important factors predictive of survival and local recurrence (Tables 1 and 2). In the regression analysis, a pass through the data was made to screen out variables and to obtain the most parsimonious model while, at the same time, using as much of the data as possible.

RESULTS

The mean age of the patients in this study was 46 ± 18 years (standard deviation) with a range from 16 to 80 years. Fifty-one per cent of patients were men, and 49% were women. Of the 182 patients with extremity sarcomas who presented to the Brigham and Women's Hospital, 145 (80%) were seen for a newly diagnosed primary sarcoma, and 25 (14%) presented with a locally recurrent sarcoma previously treated at another institution. Ten patients (5%) in this series presented with metastatic dis-

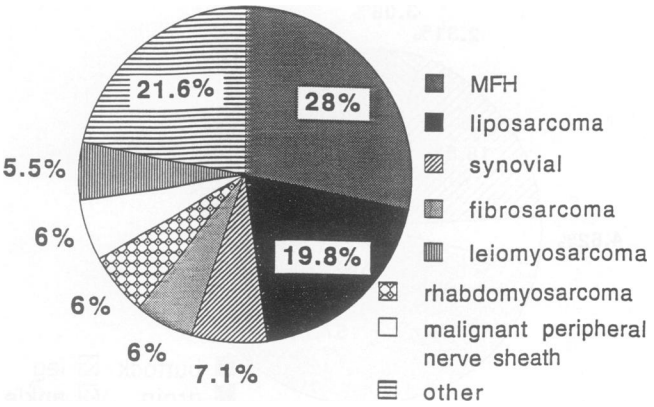

Figure 2. Distribution of sarcomas by histologic type.

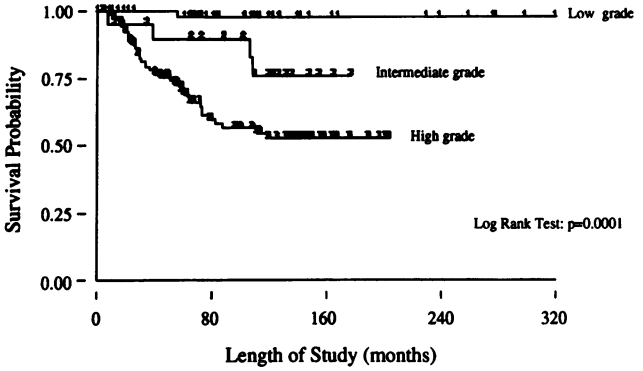

Figure 4. Overall survival by grade for extremity sarcoma.

ease, and two (1%) presented with local recurrence and distant metastasis. As expected, 146 (80%) of all extremity sarcomas were proximal in location. The most common location in the lower extremity was the thigh (75 of 130 [58%]) followed by the lower leg (24 of 130 [18.5%]). For the upper extremity, the upper arm was the most common site (23 of 52 [44%]) followed by the shoulder (in 17 of 52 [33%]). The graphs in Figure 1 show the distribution of lower (Fig. 1A) and upper (Fig. 1B) extremity sarcomas by location.

Histopathologic Factors for Survival

Malignant fibrous histiocytoma (51 of 182 [28%]) and liposarcoma (36 of 182 [20%]) was the most common histologic type seen in this series of patients. There was a roughly equal distribution (approximately 6% for each) of fibrosarcoma, synovial sarcoma, rhabdomyosarcoma, leiomyosarcoma, and malignant peripheral nerve sheath tumor (Fig. 2). Forty-eight per cent of all extremity sarcomas were less than 5 cm in size, 30% were between 5 and 10 cm in size, and 22% were greater than 10 cm in size. Fifty-seven per cent or 103 of 182 of the extremity sarcomas were high grade. Twenty-nine per cent were low-grade sarcomas. The remainder of the tumors were of intermediate-grade histologic type (n = 25 [13.7%]).

The overall survival rates of the 170 patients who presented to the Brigham and Women's Hospital with either primary disease only (142 of 170, group 0) and local recurrence only (24 of 170, group 1) were found to be 72 ± 6% and 57 ± 12%, respectively, at 12 years as shown in the Kaplan–Meier survival curves in Figure 3. Although there was a trend for a decreased 12-year survival rate for the locally recurrent sarcomas, there was no statistical difference in survival between these two groups by log-rank testing (p = 0.658).

In this series, we found that grade was a significant predictor of survival (p = 0.0001, by log-rank test). Figure 4 shows the Kaplan–Meier survival curves for low-grade, intermediate-grade, and high-grade tumors with 12-year survival rates of 98 ± 4%, 76 ± 12%, and 52 ± 6%, respectively. The size of the sarcoma was another important predictor of overall survival with sarcomas less than 5 cm in size having a 12-year overall survival probability of 83 ± 6% compared with a 52 ± 15% survival probability for sarcomas larger than 10 cm. Figure 5 shows the

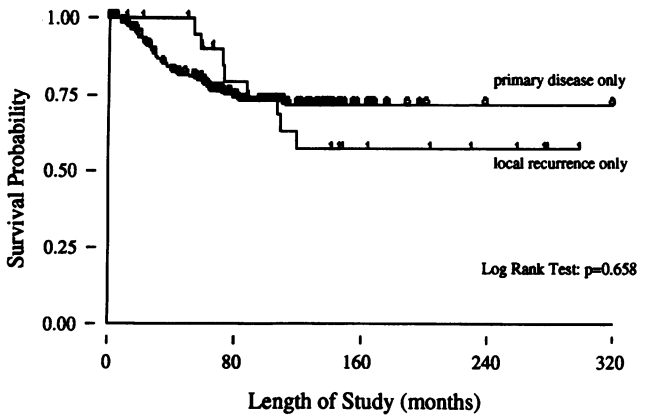

Figure 3. Overall survival by status at presentation.

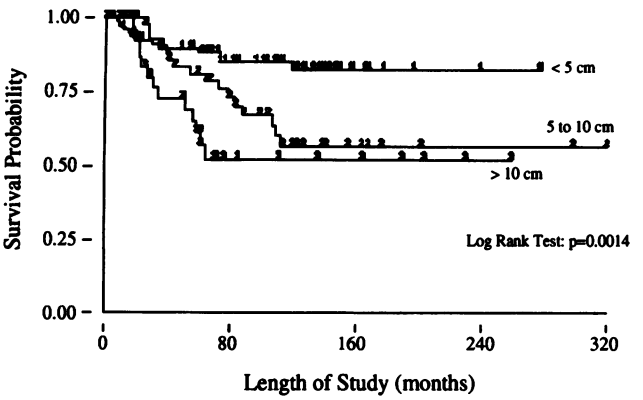

Figure 5. Overall survival by size for extremity sarcoma.

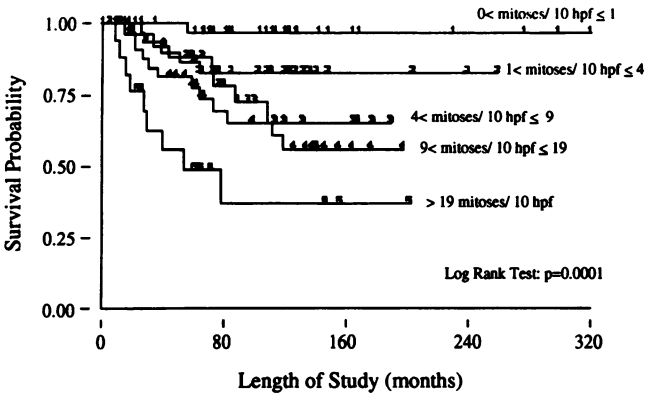

Figure 6. Overall survival by mean number of mitoses per 10 hpf for extremity sarcoma.

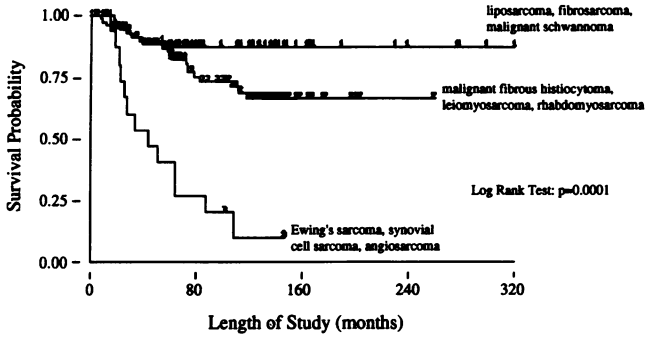

Figure 7. Overall survival by histologic type of extremity sarcoma.

survival curves for tumors less than 5 cm, 5 to 10 cm, and greater than 10 cm. These survival distributions are significantly different (p = 0.0014, by log-rank test).

In addition to grade and size, we found that the mitotic activity of the tumor (as measured by the mean number of mitoses per 10 hpf) correlated with the survival probability. The patients with extremity sarcomas were divided into five groups based on the mean number of mitoses per 10 hpf as follows: group 1 (0 to 1/10 hpf), group 2 (1 to 4/10 hpf), group 3 (4 to 9/10 hpf), group 4 (9 to 19/10 hpf), and group 5 (> 19/10 hpf). The overall survival probability for these five different groups of mitotic activity is shown in Figure 6. The survival distributions were significantly different (p = 0.0001, by log-rank test). The 12-year overall survival probability for groups 1 through 5 were 96 ± 6%, 83 ± 12%, 65 ± 13%, 56 ± 10%, and 36 ± 14%, respectively.

The histologic type was also an important determinant of survival. Liposarcoma, fibrosarcoma, and malignant peripheral nerve sheath tumor had a 12-year survival probability of 88 ± 6% compared with angiosarcoma, synovial sarcoma, and Ewing's sarcoma, which had a 12-year survival probability of 10 ± 9%. The overall survival for patients with malignant fibrous histiocytoma, leiomyosarcoma, and rhabdomyosarcoma was 67 ± 8%, thus making an intermediate-risk group. These three groups of histologic types had significantly different survival distributions (Fig. 7; p = 0.0001, by log-rank test).

Treatment Factors Influencing Survival and Local Recurrence

The majority of patients (75%) were treated with wide local excisions, 19% required radical compartmental resections, and 6% required amputation. There was no significant difference in survival or local recurrence between these three types of surgical resection. The probability of being free of local recurrence at 12 years for patients presenting to us with primary or locally recurrent sarcomas was 87.5 ± 8% for the amputation group, 82.5 ± 11% for the radical compartmental resection group, and 80 ± 6% for the group treated with wide local excision with or without radiation therapy. The presence of clean margins as opposed to microscopically positive margins at the time of definitive resection did not influence the overall survival. However, if clean margins were obtained, the first local recurrence-free rate was 83 ± 6% compared with 67 ± 11% if there were microscopically positive margins. This difference in local recurrence rate was significant (p = 0.031, by log-rank test). If the margin obtained at the time of definitive resection was greater than 1 cm, then the first local recurrence-free rate was 100%.

Postoperative adjuvant radiation therapy was used in 42% of patients with primary or locally recurrent soft tissue sarcoma in this series. Fifty-two per cent of patients received no adjuvant radiation therapy, and 6% of patients received preoperative radiation therapy. We found no statistical difference in overall survival or local recurrence rates between the patients treated with preoperative radiation, postoperative radiation, or no radiation. Adjuvant radiation was used in 9 of 50 patients (18%) with low-grade sarcomas, 13 of 21 (62%) with intermediate-grade sarcoma, and 69 of 93 (74%) with high-grade sarcomas. Of the nine patients with low-grade sarcomas who received postoperative radiation therapy, all had less than a 0.5-cm margin on definitive primary resection. There was only one local recurrence in this group of low-grade sarcomas treated with adjuvant radiation, and this was in the only patient who had microscopically positive margins. In the group of 41 patients with low-grade sarcomas who did not receive adjuvant radiation therapy, there were 6 local recurrences. All these patients had clean but close margins ranging from 0.05 to 0.5 cm. The Kaplan–Meier 12-year local recurrence-free rate was 86 ± 6% for the patients with low-grade sarcomas who were not treated with adjuvant radiation therapy compared with 83 ± 15% for the small group of low-

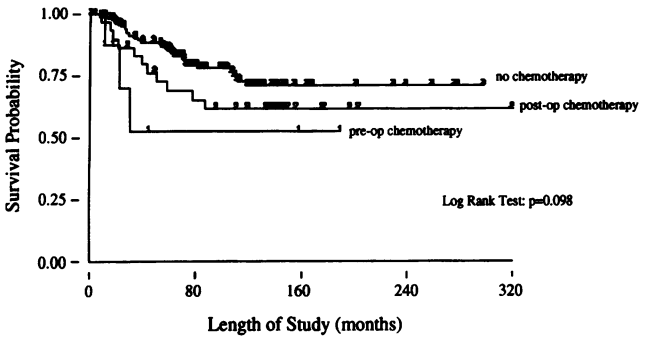

Figure 8. Adjuvant chemotherapy: effects on overall survival for extremity sarcoma.

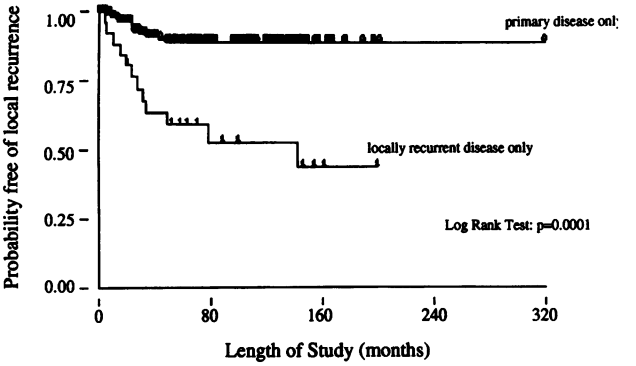

Figure 9. First local recurrence-free rate by status on presentation to Brigham and Women's Hospital.

grade sarcomas that received adjuvant radiation (p = 0.98, by log-rank test). For the high-grade sarcomas, the 12-year local recurrence-free rate for the 69 patients treated with adjuvant radiation therapy was 88 ± 4% compared with 75 ± 10% for the 24 patients who received no radiation therapy. This difference was not statistically significant by log-rank analysis; however, it approached significance with p = 0.1.

The majority of patients (76%) received no adjuvant chemotherapy; 19% of patients received adjuvant postoperative chemotherapy, and 5% received preoperative chemotherapy. Figure 8 shows the Kaplan–Meier survival curves for each of these treatment groups. The 12-year survival rate for the no-chemotherapy group was 71 ± 7%; for the postoperative adjuvant chemotherapy group, 62 ± 10%; and for the preoperative chemotherapy group, 53 ± 22% (p = 0.098, by log-rank test). However, as a subsequent multivariate analysis will show, the postoperative chemotherapy group and no-chemotherapy group were not equivalent. There were a greater proportion of high-grade tumors, larger than 10 cm, in the chemotherapy treatment arm. For example, 87% of sarcomas were high grade, and 30% were larger than 10 cm in size in the group of patients treated with postoperative adjuvant chemotherapy compared with 46% of sarcomas with a high-grade histologic type and 17% greater than 10 cm in size in the group not treated with chemotherapy.

Identification of Prognostic Factors

Overall Survival

Multivariate Cox regression analysis yielded five possible predictors (Table 1) in which the probabilities of the univariate Wald ratio statistics were all less than 0.05 (score test statistic = 71.01 with 5 degrees of freedom, p = 0.0001). For survival, size greater than 10 cm carried a hazard ratio of 3.4 after having adjusted for the other four prognostic factors; it was significant at the p = 0.006 level. We found that sarcomas of the following histologic types: angiosarcoma, synovial sarcoma, and Ewing's sarcoma, were associated with a hazard ratio of 12.7 (adjusted for other prognostic factors) with significance at the p = 0.0001 level. The mean number of mitoses per 10 hpf was used as a continuous variable in this model, and thus, for a 1-unit rise in the mean number of mitoses per 10 hpf, we would see a proportional change in the hazard ratio by 1.06 (adjusted for other prognostic factors). The mitotic activity in this model was found to be an additional prognostic variable (p = 0.005). High grade was also found to be a significant predictor of survival (p = 0.018), having a hazard ratio of 4.76 (adjusted for other prognostic factors) in this model. The age at diagnosis used as a continuous variable in this model was found to be a prognostic variable for survival (p = 0.016).

Local Recurrence

The status on presentation to us (primary disease only or locally recurrent disease only) and the margins achieved at definitive surgical resection were the only two important prognostic factors for local recurrence identified in this study. Locally recurrent sarcomas were found to have a 7.4-fold greater risk of local recurrence compared with primary sarcomas on presentation to us, and this difference was significant at the p = 0.0001 level. The local recurrence-free rate was 89 ± 5% for patients presenting to us with primary disease only compared with 53 ± 15% if patients presented to us with local recurrence only (Fig. 9). Patients with microscopically positive margins on definitive surgical resection had a 2.4-fold greater risk of local recurrence than did those who had clean margins on surgical resection (p = 0.052). The size, grade, histologic type, mitotic activity, type of initial biopsy, and extent of surgical resection (amputation *vs.* wide excision *vs.* compartmental) had no statistically significant effect on local recurrence by multivariate analysis using a Cox proportional-hazards model.

DISCUSSION

The present study demonstrated the importance of grade, size, mitotic activity, and histologic subtype as prognostic factors for survival in extremity soft tissue sarcoma. In the present study, we found that sarcomas larger than 10 cm in size carried a 3.4-fold greater probability of death compared with sarcomas that were less than 5 cm in size ($p = 0.006$). Grade and size have been identified as important prognostic factors in previous studies[20–26] and used in a variety of staging systems.

The utility of mitotic activity separate from grade has not previously been appreciated to our knowledge. In our multivariate analysis, we found that high-grade sarcomas had a 4.8-fold increase in the risk of death compared with low-grade sarcomas ($p = 0.018$) and that mitotic activity (as determined by the mean number of mitoses per 10 hpf) could be used as an additional prognostic factor ($p = 0.005$). Using the number of mitoses as a continuous variable for every unit change in mitotic activity, there was a corresponding 1.06-fold increase in the risk of death. Most pathologists determine that the sarcoma grade is low, intermediate, or high from a qualitative assessment of tumor cellularity, necrosis, cellular pleomorphism, and the degree of differentiation. The advantage of using the mean number of mitoses per 10 hpf as a prognostic indicator is that this can be more accurately quantified and should, therefore, be pathologist independent if careful attention is paid to a number of important details. In addition to mean mitotic activity, we also examined the utility of using the maximum number of mitoses per 10 hpf. However, we found that the mean mitotic activity is a better predictor of survival than the maximum mitotic activity, especially in tumors with relatively low mitotic counts in the less than ten range.

In addition to the assessment of grade and mitotic activity, the histologic subtype of sarcoma was found to be an important determinant of survival. A histologic diagnosis of angiosarcoma, synovial sarcoma, or Ewing's sarcoma carried with it a 13-fold increased risk of death compared with liposarcoma, fibrosarcoma, and malignant peripheral nerve sheath histologic types ($p = 0.0001$). This result continues to emphasize the importance of an accurate histologic diagnosis from whatever method of biopsy is used before definitive treatment. Although we studied small numbers of patients, given such a poor prognosis, those diagnosed with angiosarcoma, synovial sarcoma, or Ewing's sarcoma would seem to benefit from entrance into adjuvant or neoadjuvant systemic trials before or after definitive surgical resection. Although malignant fibrous histiocytoma, leiomyosarcoma, and rhabdomyosarcoma had a worse survival than did liposarcoma, fibrosarcoma, and malignant peripheral nerve sheath histologic types, this was not statistically significant in our multivariate analysis. Although other studies have shown differences in survival by histologic type, these differences were not shown to be independent of other clinical pathologic factors in a multivariate analysis.

The use of postoperative adjuvant chemotherapy in the treatment of extremity soft tissue sarcomas continues to be controversial. In the present study, we found no difference in the overall survival of patients who received preoperative or postoperative chemotherapy compared with the group that received no adjuvant therapy by the log-rank test. Although there were small numbers of patients, the multivariate analysis showed no significant risk or benefit for overall survival in the group of patients receiving preoperative or postoperative adjuvant chemotherapy. Future randomized chemotherapy trials should be directed at patients with large, high-grade tumors with high mitotic activity. We might even consider selecting patients with a mean mitotic activity exceeding 9 mitoses per 10 hpf, irrespective of size. In our series, tumors less than 5 cm with greater than 9 mitoses per 10 hpf had a 12-year survival rate of 68%, whereas extremity sarcomas less than 5 cm with 0 to 9 mitoses per 10 hpf had a 94% 12-year survival rate. High-grade sarcomas with less than 9 mitoses per 10 hpf that were larger than 5 cm in size were associated with a 47% 12-year survival rate. Thus, extremity sarcomas of any size with a mean mitotic activity greater than 9 mitoses per 10 hpf or high-grade tumors greater than 5 cm in size (regardless of mitotic activity) would be likely candidates for possible entrance into randomized adjuvant trials.

Survival was not found to be affected by status on presentation (primary *vs.* local recurrence), type of surgical resection, or whether clean or microscopically positive margins were achieved at the time of surgical resection. Thus, local recurrence does not appear to play a major role in influencing the overall survival. The only prognostic factors predictive for local recurrence were whether the patient presented to us with a locally recurrent sarcoma ($p = 0.0001$) or had microscopically positive margins at the time of definitive surgical resection ($p = .052$); these had hazard ratios of 7.4 and 2.4, respectively. Unlike other studies,[20,21,23] we showed no association between the size, grade, and histologic type of the tumor and the propensity for local recurrence. The ability to attain clean surgical margins seems to be the most important factor to consider in performing limb-sparing surgery. In these low-grade sarcomas, if a greater than 1-cm margin of resection was obtained, there were no local recurrences in this group even when the patient did not receive adjuvant radiation therapy. Among low-grade sarcomas with clean but less than 0.5-cm margins that were not treated with postoperative radiation therapy,

there were 6 local recurrences. These data suggest that, for low-grade sarcomas in which a 1-cm margin can be achieved, adjuvant radiation therapy is not necessary for local control. However, there does appear to be a role for postoperative radiation therapy for low-grade sarcomas if the closest margin is less than 1 cm. We believe the utility of postoperative radiation therapy on local recurrence for low-grade sarcomas should be examined in a randomized trial for this subset of patients. The local recurrence rate for our patients with primary low-grade sarcoma was 13%.

In high-grade sarcomas, the role of postoperative radiation therapy and limb-sparing surgery has been well established, and the efficacy of this approach was demonstrated by our study, which showed a local recurrence rate of only 9.2% for patients with primary high-grade sarcomas so treated. This excellent local control rate was achieved with the use of postoperative external beam radiation therapy and was similar to the results achieved with brachytherapy for high-grade extremity sarcomas.[27,28] The optimal extent of surgical resection and the extent of radiation field size required for local control remains controversial. The recent brachytherapy trials from Memorial Sloan-Kettering Cancer Center suggest that, for high-grade tumors, just the surgical tumor bed needs to be treated to achieve a local recurrence rate of 10%.[27,28] Future trials addressing the minimal field size required for postoperative radiation therapy to achieve optimal local control need to be performed.

Future improvements in outcome will come from identifying the subset of patients most likely to benefit from chemotherapy. Up-front neoadjuvant chemotherapy for 3 cycles for sarcomas with greater than 9 mitoses per 10 hpf; Ewing's, angiosarcoma, or synovial sarcoma histologic types; or size greater than 10 cm would permit the assessment of the initial response. Responders could be treated with surgical resection of the primary followed by three to four more cycles of postoperative adjuvant chemotherapy. Nonresponders would be treated with surgery alone and spared potentially toxic postoperative chemotherapy.

In summary, as in other large series of extremity sarcomas,[20,21,23,29] we showed that grade, size, age, and histologic subtype were important prognostic factors in predicting overall survival. However, for the first time to our knowledge, we found that the mean mitotic activity was an additional risk factor. As in other series, we did not show a significant improvement in overall survival with postoperative adjuvant chemotherapy in this nonrandomized series of patients either by univariate or multivariate analysis. However, the use of mitotic activity along with size, grade, and histologic type will allow us potentially to identify a subpopulation of patients that might form the basis of future systemic neoadjuvant or adjuvant trials.

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